VEGF-B could be an ideal candidate as therapy of dilated cardiomyopathy which is characterized by an increased rate of apoptosis and cardiac remodeling. The aim of this current pre-clinical large animal study was to determine if antegrade gene therapy with VEGF-B can help to prevent the onset of pacing-induced cardiomyopathy.
Methods: The possible effects of VEGF-B gene therapy were tested in 23 chronically instrumented dogs with tachypacing-induced dilated cardiomyopathy and a pacing protocol of four weeks. Thirteen subjects received at least 10^13 AAV-9-VEGF-B167 genes intracoronarily administered with a 2.5F micro-infusion catheter selectively into the LAD at the beginning of the pacing protocol. Ten dogs received 10^13 AAV9-GFP instead and served as control group. Gene transduction efficacy was measure by GFP-staining after the completion of the protocol. Hemodynamic changes and echocardiography were compared at baseline and after 28days of pacing.
Results: Gene transfer procedures were successful in all animals. The GFP-infection rate of cardiomyocytes varied widely from 1%-50% with heterogeneous distribution between subendocardial, midventricular and subepicardial layers. But the VEGF-B treatment helped to preserve cardiac function significantly compared to the GFP control group thus LV end-diastolic pressure was 12.3±3.6 vs. 23.3±34.1mmHg, dP/dtmax 2432±732 vs. 1461±548mmHg/sec and ejection fraction 48.2±4.8 vs. 30.4±5.4% (all $P<0.05$). We were able to identify a reduction of oxidative stress in vivo and in vitro as possible mechanism of cardiprotection of VEGF-B in addition to the known anti-apoptotic capacity in the treatment group.
Conclusions: These results, obtained with a clinical applicable interventional approach in an established animal model of heart failure, support that VEGF-B167 gene therapy is highly effective as new therapy for non-ischemic heart failure.

TCT-823

Results from LateTIME: A Randomized, Placebo Controlled Trial of Intracoronary Stem Cell Delivery Two to Three Weeks Following Acute Myocardial Infarction from the Cardiovascular Cell Therapy Research Network

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Background: Meta-analysis suggest that intracoronary (IC) administration of autologous bone marrow mononuclear cells (BMCs) delivered early after acute myocardial infarction (MI) may improve left ventricular (LV) function. However, many patients early post MI are unstable or present to sites without cell delivery capabilities, and it is unknown if changes in the myocardium or bone marrow will alter the homing and engraftment of BMCs when delivered several weeks post-MI. LateTIME was a randomized, double-blind, placebo-controlled trial sponsored by the National Heart, Lung and Blood Institute (NHLBI) and CCTRN to investigate safety and therapeutic efficacy of IC BMCs delivered 2-3 weeks following successful reperfusion with primary PCI in patients with new post-MI LV dysfunction. At 6 months, LVEF improved in both groups with no significant difference between groups but with a trend for improvement in clinical events in BMC-treated patients (5%) vs. placebo (17%). We will report the 2-year MRI and clinical results.
Methods: A total of 87 (72 M, 15 F) age 57±11 underwent bone marrow aspiration and isolation of BMCs using standardized automated system (Sepax device, Biosafe SA) followed by IC infusion of 150 million BMCs or cell-free solution (2:1 BMC:Placebo) within 12 hours of bone marrow harvest in a blinded fashion at 5 CCTRN sites and their satellites between September 2008 and February 2011. Changes in global and regional LV function by cardiac MRI were assessed at 6 months (1° endpoint) as well as 1 and 2 years, in addition to clinical events
Results: Results will be presented at TCT 2013.
Conclusions: In the LateTIME trial, patients treated 2-3 weeks post MI had no significant improvement in LV global or regional function at 6 months with a trend for reduction in clinical events complete and final. Two-year global and regional function as well as clinical events will be presented for the LateTIME trial.

TCT-824

Improved Safety And Efficacy Of A Novel Dual cRGD- And Everolimus-coated Coronary Stent Compared To Everolimus-eluting Stents In The Porcine Model

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Background: Drug-eluting stents markedly reduce restenosis; however, re-endothelialization is delayed. Integrin-binding cyclic Arg-Gly-Asp (cRGD) peptide-loaded stents offer potential for enhanced early and late endothelial recovery by endothelial progenitor cell (EPC) anchorage. Here, a novel dual cRGD and everolimus-eluting stent was compared to an everolimus-eluting stent.
Methods: The porcine 10% coronary overstretch model was employed for analysis of Multi-Link Tetra bare metal stents with or without a specific adherent, conformal, mechanically robust polymer coating based on an aromatic polyetherurethaneurea with a soft segment of polytetramethyleneoxide and a hard segment of diphenylmethane diisocyanate and mixed diamines covered by a control-release layer. Stents were coated with immobilized cRGD, everolimus or cRGD + everolimus on the biostable PEA-40 polymer surface coating. Isolated porcine EPCs were labeled with cell tracker CM-DiI and infused into coronary arteries immediately after stent implantation. cRGD or everolimus recovered mass were analyzed by mass spectroscopy, the luminal area was inspected by en face fluorescence microscopy or scanning electron microscopy for re-endothelialization and area stenosis was quantified.
Results: cRGD and everolimus recovered mass from PEA-40 cRGD/everolimus stents showed a slow release profile. EPC recruitment to stents was evidenced after intracoronary infusion of fluorescence-labeled EPCs. In cRGD + everolimus loaded stents, in-stent cross sectional stenosis was reduced and re-endothelialization above stent struts was accelerated ($p<0.05$ for both) while re-endothlialization between struts was similar ($p>0.05$) as compared to both everolimus-loaded and bare-metal stents.
Conclusions: PEA 40 is a reliable carrier for cRGD and everolimus. cRGD + everolimus coated stents decrease coronary stenosis and promote endothelialization compared to everolimus-eluting stents. Dual-loaded stents combine accelerated integrin-dependent endothelial strut coverage with everolimus-dependent stenosis reduction. Vascular healing by distinct homing of circulating EPCs and antiproliferatory properties of everolimus concertedly act to improve stent safety and efficacy.

TCT-825

In-Vivo Long Term Evaluation of a Novel Mitral Valve Regurgitation Therapy: Experience in a Preclinical Large Animal Model

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Background: The MitraSpacer™ (Cardiosolutions, Inc.) is a novel approach to address mitral regurgitation by introducing a dynamic spacer with characteristics that constantly adjust to the instantaneous hemodynamics of the mitral apparatus and left atrium (LA). The purpose of this study was to evaluate the safety of the MitraSpacer™ within the mitral valve apparatus in the domestic swine model.
Methods: Five (5) domestic swine were enrolled in this study. Through a left thoracotomy, the shaft of the MitraSpacer™ was introduced through the left ventricular (LV) apex and advanced in to the left atrium avoiding the chordae tendineae. Once the device was in place, the balloon located in the distal portion of the shaft was partially filled with an iopromide/saline mix introduced by a subcutaneous access port to the desired volume. After implantation, all animals were survived up to 90 days and heart and device were examined for further histological analysis.
Results: Following implantation, device performance was assessed by fluoroscopy and echocardiography. The volume within the balloon shifted during the cardiac cycle in all cases following the direction of blood flow and applied pressure. All enrolled animals survived up to 90 days for terminal imaging and tissue harvest. Echo data showed no change in LV ejection fraction from baseline to 90 days, 60.6±4.7% and 65.7±7.8% ($p=0.34$) respectively, and slight changes in LA and LV volumes consistent with the rate of growth of the animal over time. In addition, there were no observations of disruption in LV diastolic function, pulmonary vein inflow, or tricuspid regurgitation. The histological analysis demonstrated minimal impact to the mitral apparatus despite constant contact with the device, and no evidence of thromboembolism in the heart and peripheral organs.
Conclusions: In a healthy animal model, the long term placement of the MitraSpacer™ was feasible, maintained cardiac performance and caused no structural changes to the mitral apparatus over 90 days.